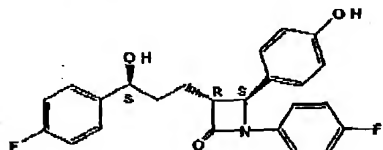


ZETIA™ (EZETIMIBE) TABLETS

DESCRIPTION

ZETIA (ezetimibe) is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related polysterols. The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-chlorophenyl)-2(5)-hydroxypropyl]-4(S)-[4-hydroxyphenyl]-2-azetidinone. The empirical formula is $C_{24}H_{27}FNO_4$, its molecular weight is 405.4 and its structural formula is:



Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 165°C and is stable at ambient temperature. ZETIA is available as a tablet for oral administration containing 10 mg of ezetimibe and the following inactive ingredients: croscarmellose sodium NF, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, polydioxane USP, and sodium lauryl sulfate NF.

CLINICAL PHARMACOLOGY

Background

Clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B), the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of high density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoprotein (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

ZETIA reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with hypercholesterolemia. Administration of ZETIA with an HMG-CoA reductase inhibitor is effective in improving mean total-C, LDL-C, Apo B, TG, and HDL-C beyond either treatment alone. The effects of ezetimibe given either alone or in addition to an HMG-CoA reductase inhibitor on cardiovascular morbidity and mortality have not been established.

Mode of Action

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. In a 2-week clinical study in 30 hypercholesterolemic patients, ZETIA inhibited intestinal cholesterol absorption by 54%, compared with placebo. ZETIA had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E (in a study of 113 patients), and did not impair adrenocortical steroid hormone production (in a study of 118 patients).

The cholesterol control of the liver is derived predominantly from three sources. The liver can synthesize cholesterol, take up cholesterol from the blood from circulating lipoproteins, or take up cholesterol absorbed by the small intestine. Intestinal cholesterol is derived primarily from cholesterol secreted in the bile and from dietary cholesterol.

Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-lowering compounds (HMG-CoA reductase inhibitors, bile acid sequestrants [resins], fibric acid derivatives, and plant sterols).

Ezetimibe does not inhibit cholesterol synthesis in the liver, or increase bile acid excretion. Instead, ezetimibe localizes and appears to act at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of HMG-CoA reductase inhibitors (see CLINICAL STUDIES).

Pharmacokinetics

Absorption

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10-mg dose of ZETIA in fasted adults, mean ezetimibe peak plasma concentrations (C_{max}) of 3.4 to 8.5 ng/mL were obtained within 4 to 12 hours (T_{max}). Ezetimibe-glucuronide mean C_{max} values of 45 to 71 ng/mL were obtained between 1 and 2 hours (T_{max}). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection. Ezetimibe has variable bioavailability; the coefficient of variation, based on inter-subject variability, was 35 to 60% for AUC values.

Effect of Food on Oral Absorption

Concurrent food administration (high fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ZETIA 10-mg tablets. The C_{max} value of ezetimibe was increased by 28% with consumption of high fat meals. ZETIA can be administered with or without food.

ZETIA™ (ezetimibe)

Distribution

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Metabolism and Excretion

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary and renal excretion. Metabolic oxidative metabolism (a phase I reaction) has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Following oral administration of 14 C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 50% of the total radioactivity in plasma. After 48 hours, there were no appreciable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 3% of the administered dose.

Special Populations

Geriatric Patients

In a multiple dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (>65 years) healthy subjects compared to younger subjects.

Pediatric Patients

In a multiple dose study with ezetimibe given 10 mg twice daily for 7 days, the absorption and metabolism of ezetimibe were similar in adolescents (10 to 16 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Gender

In a multiple dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in women than in men.

Race

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians. There were too few patients in other racial or ethnic groups to permit further pharmacokinetic comparisons.

Hepatic Insufficiency

After a single 10-mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe were increased approximately 2.4-fold and 2.4-fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency, the mean AUC values for total ezetimibe and ezetimibe were increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients (see CONTRAINDICATIONS and PRECAUTIONS, Hepatic Insufficiency).

Renal Insufficiency

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=6; mean $CrCl$ 30 mL/min/1.73 m²), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5-fold, compared to healthy subjects (n=9).

Drug Interactions (see also PRECAUTIONS, Drug Interactions)

ZETIA had no significant effect on a series of probe drugs (cyclosporin, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C9, and 3A4) in a "cocktail" study of twelve healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

Warfarin: Concurrent administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males.

Digoxin: Concurrent administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of digoxin and the ECG parameters (HR, PR, QT, and QTc intervals) in a study of twelve healthy adult males.

Simvastatin: Concurrent administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of simvastatin and prothrombin time in a study of twelve healthy adult males.

Oral Contraceptives: Co-administration of ezetimibe (10 mg once daily) with oral contraceptives had no significant effect on the bioavailability of ethinyl estradiol or levonorgestrel in a study of eighteen healthy adult females.

Ezetimibe: Multiple doses of ezetimibe (400 mg twice daily) had no significant effect on the oral bioavailability of ezetimibe and total ezetimibe in a study of twelve healthy adults.

Atorvastatin: In a study of twelve healthy adults, a single dose of atorvastatin (20 mg) administered had no significant effect on the oral bioavailability of total ezetimibe, ezetimibe-glucuronide, or ezetimibe based on AUC values. The C_{max} value of total ezetimibe was decreased by 20%.

ZETIA™ (ezetimibe)

Glipizide: In a study of twelve healthy adult males, steady-state levels of ezetimibe (10 mg once daily) had no significant effect on the pharmacokinetics and pharmacodynamics of glipizide. A single dose of glipizide (10 mg) had no significant effect on the exposure to total ezetimibe or ezetimibe.

HMG-CoA reductase inhibitors: In studies of healthy hypercholesterolemic (LDL-C 2150 mg/dL) adult subjects, concurrent administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of either lovastatin, simvastatin, pravastatin, atorvastatin, or fluvastatin. No significant effect on the bioavailability of total ezetimibe and ezetimibe was demonstrated by either lovastatin (20 mg once daily), pravastatin (20 mg once daily), atorvastatin (10 mg once daily), or fluvastatin (20 mg once daily).

Ezetimibe: In a study of thirty-two healthy hypercholesterolemic (LDL-C 2150 mg/dL) adult subjects, concurrent ezetimibe (200 mg once daily) administration increased the mean C_{max} and AUC values of total ezetimibe approximately 64% and 48%, respectively. Pharmacokinetics of ezetimibe were not significantly affected by ezetimibe (10 mg once daily).

Ezetimibe: In a study of forty healthy hypercholesterolemic (LDL-C 2150 mg/dL) adult subjects, concurrent ezetimibe (4 g twice daily) administration decreased the mean AUC values of total ezetimibe and ezetimibe approximately 55% and 60%, respectively.

ANIMAL PHARMACOLOGY

The hypercholesterolemic effect of ezetimibe was evaluated in cholesterol-fed Rhesus monkeys, dogs, rats, and various models of human cholesterol metabolism. Ezetimibe was found to have an ED₅₀ value of 0.3 mg/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED₅₀ values in dogs, rats, and mice were 7, 36, and 700 mg/kg/day, respectively. These results are consistent with ZETIA being a potent cholesterol absorption inhibitor.

In a rat model, where the glucuronide metabolism of ezetimibe (SCH-60663) was administered intraduodenally, the metabolite was as potent as the parent compound (SCH-58236) in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug.

In 1-month studies in dogs given ezetimibe (0.03-300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased 2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14-day study in mice given ezetimibe (0.3-5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

A series of acute practical studies was performed to determine the selectivity of ZETIA for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of C14 cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, diethyl estradiol, or the fat-soluble vitamins A and D.

In 4- to 12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with HMG-CoA reductase inhibitors (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

CLINICAL STUDIES

Primary Hypercholesterolemia

ZETIA reduces total-C, LDL-C, Apo B, and TG, and increases HDL-C in patients with hypercholesterolemia. Minimal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy.

ZETIA is effective in patients with hypercholesterolemia, in men and women, in younger and older patients, alone or administered with an HMG-CoA reductase inhibitor. Experience in pediatric and adolescent patients (ages 9 to 17) has been limited by patients with homozygous familial hypercholesterolemia (HoFH) or abetalipoproteinemia.

Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of ZETIA.

Monotherapy

In two, multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, ZETIA significantly lowered total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to placebo (see Table 1). Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

Table 1
Response to ZETIA in Patients with Primary Hypercholesterolemia
(Mean % Change from Baseline) (see text)

Treatment group	N	Total-C	LDL-C	Apo B	TG	HDL-C
Study 1*	Placebo	205	+1	+1	-1	-1
	Ezetimibe	622	-12	-18	-15	+7
Study 2*	Placebo	226	+1	+1	-1	-2
	Ezetimibe	625	-12	-18	-15	+8
Pooled Data†	Placebo	431	0	+1	-2	-2
(Study 1 & 2)	Ezetimibe	1248	-12	-18	-15	+7

*See Appendix, Studies 1 and 2, pages 10-11.

†Based on 10 mg once daily dosing.

*ZETIA significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to placebo.

Combination with HMG-CoA Reductase Inhibitors

ZETIA Added to On-going HMG-CoA Reductase Inhibitor Therapy

In a multicenter, double-blind, placebo-controlled, 8-week study, 709 patients with primary hypercholesterolemia, known coronary heart disease or multiple cardiovascular risk factors who were already receiving HMG-CoA reductase inhibitor monotherapy, but who had not met their NCEP ATP II target LDL-C goal were randomized to receive

ZETA™ (continued)

INDICATIONS AND USAGE

Primary Hypercholesterolemia

Monotherapy

ZETIA, administered alone is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Combination therapy with HMG-CoA reductase inhibitors

ZETIA, administered in combination with an HMG-CoA reductase inhibitor, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary hypercholesterolemia and non-familial hypertriglyceridemia.

The combination of ZETIA and atorvastatin or simvastatin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoHt, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Nonparametric Statistical Tests

ZETIA is indicated as adjunctive therapy to diet for the reduction of elevated cholesterol and triglyceride levels in patients with homozygous familial hypercholesterolemia.

Therapy with lipid-lowering agents should be a component of multiple risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-lowering agents should be used in addition to an appropriate diet (including restriction of saturated fat and cholesterol) and when the response to diet and other non-pharmacological measures has been inadequate. (See NCEP Adult Treatment Panel (ATP) II Guidelines, summarized in Table 2.)

Table 7
Summary of Self-Appraisal of Satisfaction

Risk Category	LDL level (mg/dL)	LDL level at which to initiate Pharmacologic Therapy (mg/dL)	LDL level at which to Consider Drug Therapy (mg/dL)
CVD or CVD risk equivalent ^a	<100	2100	2120 (100-125 drug optimality) ^b
10-year risk >20% ^a	<100	2120	10-year risk 10-20%: 2120 ^c 10-year risk >10%: 2100 ^c
0-1 Risk factor ^a	<100	2150	2150 (100-199: LDL-lowering drug)

[illegible][illegible]

Walter had earlier furnished a list of individuals that mostly L.A. County residents were attending, approximately 200-250,000 on the day of the anti-nuclear demonstration, from 1961, approximately 1962-1963. Family history of MEMPHIS and L.A. to make that degree reliable. (28 pages); (29) to include that degree reliable (28 pages); (30) from 1962 pages written that time, 1962, approximately 200 pages, stated as a "roughness" of the pages; (31) from 1962 pages written that time, from that time that date.

* Almost all people with 10-15 day before from a 1962-1963 date; from 1962-1963 approximately 100 pages from 10-15 day before from 1962-1963.

Prior to initiating therapy with ZETIA, secondary causes for dyslipidemia (i.e., diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C [pyrazinamide, amphotericin, steroids, and corticosteroids]), should be excluded or, if appropriate, treated. A lipid profile should be performed to measure total-C, LDL-C, HDL-C and TG. For TG levels ≥ 400 mg/dL (≥ 4.5 mmol/L), LDL-C measurement should be delayed and lipids treated with fibrates.

At the time of hospitalization for an acute coronary event, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge.

CONTINUATION:

The combination of ZEXIA with an HMG-CoA reductase inhibitor is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When ZETA is administered with an HMG-CoA reductase inhibitor to a woman of childbearing potential, refer to the pregnancy category and product labeling for the HMG-CoA reductase inhibitor. (See PRECAUTIONS, Pregnancy.)

PRECAUTIONS

Concurrent administration of ZETIA with a specific HMG-CoA reductase inhibitor should be in accordance with the product labeling for that HMG-CoA reductase inhibitor.

Link Expression

In controlled clinical monotherapy studies, the incidence of consecutive elevations ($\geq 3 \times$ the upper limit of normal [ULN]) in serum transaminases was similar between ZERA (0.5%) and placebo (0.2%).

In controlled clinical combination studies of ZETIA initiated concomitantly with an HMG-CoA reductase inhibitor, the incidence of consecutive elevations ($\geq 3 \times \text{ULN}$) in serum transaminases was 1.3% for patients treated with ZETIA administered with HMG-CoA reductase

ZETA Initiated Concurrently with an HMG-CoA Reductase Inhibitor

In four, multicenter, double-blind, placebo-controlled, 12-week trials, in 2382 hypercholesterolemic patients, ZETIA or placebo was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin.

When all patients receiving ZETA with an HMG-CoA reductase inhibitor were compared to all those receiving the corresponding HMG-CoA reductase inhibitor alone, ZETA significantly lowered total-C, LDL-C, Apo B, and TG, and, with the exception of pravastatin, increased HDL-C compared to the HMG-CoA reductase inhibitor administered alone. LDL-C reductions induced by ZETA were generally consistent across all HMG-CoA reductase inhibitors. (See footnote c, Tables 3 to 8.)

Treatment (Daily Dose)	E	Total-C	LMC-C	Age-B	TIF	ACE-C
Placebo	59	+4	+4	-2	-2	+2
ZETA	55	-14	-20	-3	-5	-4
Alcortesta 18 mg	60	-25	-27	-18	-21	-6
ZETA + Alcortesta 10 mg	65	-38	-53	-43	-31	-8
Alcortesta 20 mg	59	-39	-42	-34	-33	-4
ZETA + Alcortesta 20 mg	62	-80	-54	-64	-59	-6
Alcortesta 40 mg	64	-32	-45	-57	-34	+4
ZETA + Alcortesta 40 mg	65	-42	-56	-45	-34	-5
Mormesta 80 mg	52	-46	-54	-56	-31	-3
ZETA + Alcortesta 80 mg	63	-46	-51	-59	-48	+7
Provera 500 (all Menorrhagia Doses)	248	-52	-44	-20	-24	+4
Provera 500 plus ZETA +	255	-41	-56	-43	-33	+7

* For hippocampus, volume % change from baseline
 * Glutamate - up on 1st 3 treatment days
 * Effect = all days of treatment period (did not significantly increase total 2, 3, 4, 5, and 7d, and increased 6d-G compared to baseline of 0d-treatment period [30-35 mg])

Heterogeneous Familial Hypercholesterolemia (HFD)

A study was conducted to assess the efficacy of ZETIA in the treatment of HcH. This double-blind, randomized, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HcH, with or without concomitant LDL apheresis, against receiving simvastatin or atorvastatin (40 mg). Patients were randomized to one of three treatment groups, atorvastatin or simvastatin (80 mg), ZETIA administered with atorvastatin or simvastatin (40 mg), or ZETIA administered with atorvastatin or simvastatin (80 mg). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine (see PRECAUTIONS), ezetimibe was dosed at least 4 hours before or after administration of resins. Mean baseline LDL-C was 341 mg/dL in those patients randomized to atorvastatin 40 mg or simvastatin 40 mg alone and 316 mg/dL in those randomized to ZETIA plus atorvastatin 40 mg or 80 mg and 300 mg/dL in those randomized to ZETIA plus atorvastatin 40 mg or simvastatin 40 and 60 mg statin groups, respectively. ZETIA reduced LDL-C (21%) compared with atorvastatin 40 mg or simvastatin 40 mg. ZETIA plus atorvastatin 40 mg or simvastatin 40 mg reduced LDL-C (21%) compared with atorvastatin 80 mg or simvastatin 80 mg. In those treated with ZETIA plus 80 mg atorvastatin or 80 mg simvastatin (7%), no reduction in LDL-C was induced by ZETIA.

Homomorphism Classification (Bijection)

A study was conducted to assess the efficacy of ZETIA in the treatment of homozygous hypercholesterolemia. One multicenter, double-blind, placebo-controlled, 8-week trial, 37 patients with homozygous familial hypercholesterolemia with elevated plasma cholesterol levels (≥ 6 mg/dL) on simvastatin control. Therapeutic regimen (risk, lipid-lowering therapy), HMG-CoA reductase inhibitors, lipid bypass surgery and/or LDL receptors were randomized to receive ZETIA (n=30) or placebo (n=7). Due to decreased bioavailability of ezetimibe in patients concurrently receiving cholestyramine (see PRECAUTIONS), ezetimibe was dosed at least 2 hours before or 4 hours after results were administered. Efficacy of the study included reduction of LDL-cholesterol, ZETIA slightly lowered plasma total cholesterol and triglycerides, and increased HDL cholesterol compared to placebo. In contrast, patients who received placebo had increases in cholesterol and triglycerides at 2 and 4 weeks from baseline, respectively. For patients treated with ZETIA, their plasma levels of all lipids were reduced progressively over the course of the study. The effects of reducing plasma cholesterol and triglycerides on reducing the risks of coronary artery disease and mortality will be established.

Reductions in cholesterol and campesterol were consistent between patients taking ZETIA concomitantly with bile acid sequestrants (n=6) and patients not on concomitant bile acid sequestrant therapy (n=21).

ZETIA™ (ezetimibe)

Inhibitors and 0.4% for patients treated with HMG-CoA reductase inhibitors alone. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. When ZETIA is co-administered with an HMG-CoA reductase inhibitor, liver function tests should be performed at initiation of therapy and according to the recommendations of the HMG-CoA reductase inhibitor.

Statistical Analysis

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ZETIA compared with the relevant control arm (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipid-lowering drugs. In clinical trials, the incidence of CPK >10 X ULN was 0.2% for ZETIA vs 0.1% for placebo, and 0.1% for ZETIA co-administered with an HMG-CoA reductase inhibitor vs 0.4% for HMG-CoA reductase inhibitors alone.

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients. (See CLINICAL PHARMACOLOGY, Special Populations.)

Drug Interactions (See also CLINICAL PHARMACOLOGY, Drug Interactions.)

Cholestyramine: Concurrent cholestyramine administration decreased the mean AUC of total ezetimibe approximately 65%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction.

Fibrates: The safety and effectiveness of ezetimibe administered with fibrates have not been established.

Fibrates may increase cholesterol secretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see ANIMAL PHARMACOLOGY). Co-administration of ZETIA with fibrates is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concurrent fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold.

Simvastatin: In a pharmacokinetic study, concurrent simvastatin administration increased total ezetimibe concentrations approximately 1.7-fold.

HMG-CoA reductase inhibitors: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin.

Cyclosporine: The total ezetimibe level increased 12-fold in one renal transplant patient receiving multiple medications, including cyclosporine. Patients who take both ezetimibe and cyclosporine should be carefully monitored.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on AUC₀₋₂₄ for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (~150 times the human exposure at 10 mg daily based on AUC₀₋₂₄ for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on AUC₀₋₂₄ for total ezetimibe).

Pregnancy**Pregnancy Category C**

There are no adequate and well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

In oral (gavage) nephrotoxicity development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryofetal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common renal ductal findings (extra pair of thoracic ribs, associated cervical vertebrae centra, shortened ribs) were observed at 9000 mg/kg/day (~10 times the human exposure at 10 mg daily based on AUC₀₋₂₄ for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 times the human exposure at 10 mg daily based on AUC₀₋₂₄ for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple dose studies of ezetimibe given in combination with HMG-CoA reductase inhibitors (statins) in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in combination therapy compared to monotherapy.

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When ZETIA is administered with an HMG-CoA reductase inhibitor in a woman of childbearing potential, refer to the pregnancy category and package labeling for the HMG-CoA reductase inhibitor. (See CONTRAINDICATIONS.)

Labor and Delivery

The effects of ZETIA on labor and delivery in pregnant women are unknown.

Nursing Mothers

In rat studies, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe is excreted into human breast milk; therefore, ZETIA should not

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be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

Pediatric Use

The pharmacokinetics of ZETIA in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ZETIA in the pediatric population is limited to 4 patients (3 to 17 years) in the statinolevel study and 5 patients (11 to 17 years) in the HoFH study. Treatment with ZETIA in children (<10 years) is not recommended. (See CLINICAL PHARMACOLOGY, Special Populations.)

Geriatric Use

Of the patients who received ZETIA in clinical studies, 948 were 65 and older (this included 208 who were 75 and older). The effectiveness and safety of ZETIA were similar between these patients and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, Special Populations, and ADVERSE REACTIONS.)

ADVERSE REACTIONS

ZETIA has been evaluated for safety in more than 4700 patients in clinical trials. Clinical studies of ZETIA (administered alone or with an HMG-CoA reductase inhibitor) demonstrated that ZETIA was generally well tolerated. The overall incidence of adverse events reported with ZETIA was similar to that reported with placebo, and the discontinuation rate due to adverse events was also similar for ZETIA and placebo.

Most Common

Adverse experiences reported in 22% of patients treated with ZETIA and at an incidence greater than placebo in placebo-controlled studies of ZETIA, regardless of causality assessment, are shown in Table 3.

Table 3^a
Clinical Adverse Events Occurring in 22% of Patients Treated with ZETIA and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Event	Placebo (%) n = 725	ZETIA 10 mg (%) n = 1691
Body as a whole - general disorders		
Pain	1.8	2.2
Gastrointestinal system disorders		
Abdominal pain	2.5	3.0
Diarrhea	3.0	3.7
Infection and infestations		
Intestinal viral	1.8	2.2
Pharyngitis	2.1	2.3
Sinusitis	2.0	2.8
Musculoskeletal system disorders		
Arthritis	3.0	3.8
Back pain	3.0	4.1
Respiratory system disorders		
Coughing	2.1	2.4

^aIncludes patients who reported adverse events with ZETIA alone reported in Table 1.

The frequency of less common adverse events was comparable between ZETIA and placebo.

Combination with an HMG-CoA reductase inhibitor

ZETIA has been evaluated for safety in combination studies in more than 2000 patients.

In general, adverse experiences were similar between ZETIA administered with HMG-CoA reductase inhibitors and HMG-CoA reductase inhibitors alone. However, the frequency of increased transaminases was slightly higher in patients receiving ZETIA administered with HMG-CoA reductase inhibitors than in patients treated with HMG-CoA reductase inhibitors alone. (See PRECAUTIONS, Liver Experiments.)

Clinical adverse experiences reported in 22% of patients and at an incidence greater than placebo in four placebo-controlled trials where ZETIA was administered alone or initiated concurrently with various HMG-CoA reductase inhibitors, regardless of causality assessment, are shown in Table 4.

Table 4^a
Clinical Adverse Events Occurring in 22% of Patients and at an Incidence Greater than Placebo, Regardless of Causality, in ZETIA/Statins Combination Studies

Body System/Organ Class Adverse Event	Placebo (%) n = 259	ZETIA 10 mg (%) n = 262	All Statins ^b (%) n = 526	ZETIA + Statins ^c (%) n = 925
Body as a whole - general disorders				
Chest pain	1.2	3.4	2.0	1.8
Dyspnea	1.2	2.7	1.4	1.8
Fatigue	1.0	1.0	1.4	2.0
Headache	5.4	6.0	7.3	6.2
Gastrointestinal system disorders				
Abdominal pain	2.3	2.7	3.1	3.3
Diarrhea	1.5	3.4	2.8	2.8
Infection and infestations				
Pharyngitis	1.3	3.1	2.5	2.3
Sinusitis	1.3	4.5	3.5	2.5
Upper respiratory tract infection	10.8	13.0	13.6	11.8
Musculoskeletal system disorders				
Arthritis	2.3	3.8	4.3	3.4
Back pain	3.5	3.4	3.7	4.3
Myalgia	4.5	5.0	4.3	4.5

^aIncludes four placebo-controlled combination studies in which ZETIA was initiated concurrently with an HMG-CoA reductase inhibitor.

^bAll Statins = all cases of HMG-CoA reductase inhibitors.

ZETIA™ (ezetimibe)**OVERDOSEAGE**

No cases of overdose with ZETIA have been reported. Administration of ezetimibe, 50 mg/day, to 15 subjects for up to 14 days was generally well tolerated. In the event of an overdose, symptomatic and supportive measures should be employed.

DOSE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving ZETIA and should continue on this diet during treatment with ZETIA.

The recommended dose of ZETIA is 10 mg once daily. ZETIA can be administered with or without food.

ZETIA may be administered with an HMG-CoA reductase inhibitor for incremental effect. For convenience, the daily dose of ZETIA may be taken at the same time as the HMG-CoA reductase inhibitor, according to the dosing recommendations for the HMG-CoA reductase inhibitor.

Patients with Hepatic Insufficiency

No dosage adjustment is necessary in patients with mild hepatic insufficiency (see PRECAUTIONS, Hepatic Insufficiency).

Patients with Renal Insufficiency

No dosage adjustment is necessary in patients with renal insufficiency (see CLINICAL PHARMACOLOGY, Special Populations).

Geriatric Patients

No dosage adjustment is necessary in geriatric patients (see CLINICAL PHARMACOLOGY, Special Populations).

Co-administration with Bile Acid Sequestrants

Dosing of ZETIA should occur either 22 hours before or 24 hours after administration of a bile acid sequestrant (see PRECAUTIONS, Drug Interactions).

HOW SUPPLIED

No. 3861 - Tablets ZETIA, 10 mg, are white to off-white, capsule-shaped tablets debossed with "414" on one side. They are supplied as follows:
NDC 66582-414-01 bottles of 30
NDC 66582-414-04 bottles of 90
NDC 66582-414-74 bottles of 500
NDC 66582-414-28 unit dose packages of 100.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). (See USP Controlled Room Temperature.) Protect from moisture.



MERCK / Schering-Plough Pharmaceuticals

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